REMARKS

Claims 1-7, 9, 13 and 14 are pending. Claims 3 and 7 has been canceled without prejudice.

Claim 1 has been amended to specify that the polymer matrix consists of polymers from the group consisting of acrylates, silicon polymers, and polyisobutylene. Support for this amendment can be found in original claim 3.

Claim 14 has been amended to use the preferred spelling for "laevulinic." No new matter is added by this amendment.

Summary of Interview

Applicants would like to thank Examiner Maewall, Examiner Duffy, and Examiner Gulledge for their comments during the telephone interview of April 12, 2012 to discuss the Office Action mailed December 15, 2011. Proposed claim amendments that distinguish the claimed dermal application system over the cited references were discussed. Applicants thank the Examiners for noting that claim 7 is not properly dependent upon claim 1 as amended. Applicants have canceled claim 7 to advance prosecution.

Copies of Declarations submitted in co-pending Application No. 10/332,547 that demonstrate unexpected results were previously submitted in the present application. Applicants were advised to submit new Declarations in this application rather than copies from another application. Applicants have therefore submitted a new Declaration by Mechtild Loebel affirming her statements made in the earlier Declarations.

Rejection Under 35 U.S.C. § 112, second paragraph

Claim 7 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claim 7 contains the trademark Eudragit® NE, which allegedly is unclear since a trademark is

used to identify the source of goods, not the goods themselves. This rejection is moot in view of the cancelation of claim 7.

Rejection Under 35 U.S.C. § 103

Claims 1-6, 9 and 13-14 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 95/05813 (WO 813) in view of US 6,280,765 to Gueret ('765). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Legal Standard

The starting point for an obviousness determination must be the Supreme Court's decision in *KSR v. Teleflex,* 550 U.S. 398 (2007), which refocuses the determination of whether a claimed invention is obvious back to the process the Court had defined in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). There, the Court had held that the obviousness determination should address four factors, all of which must be considered, though not in any prescribed order: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any secondary considerations suggesting nonobviousness, such as commercial success, failure of others, and long felt but unmet need. *Id.* The Court cautioned that the fact finder should be careful about reading the teachings of the invention at issue into the prior art, to avoid applying inappropriate hindsight, *ex post* reasoning. *Id. at 36.*

Even where the prior art suggests or motivates an inventor to develop the composition or process at issue, the Federal Circuit continues to recognize that there is a critical question under 35 U.S.C. § 103 as to whether the combined teachings of the prior art "would have given rise to a reasonable expectation of success" in achieving what is claimed. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

Analysis

According to the Office Action, WO 813 teaches a pharmaceutical composition comprising aminolevulinic acid (ALA) applied to the skin and indicates a desire for the ALA preparation to be stable due to the normally rapid degradation of ALA. The Office Action recognized that WO 813 does not teach crystalline ALA suspended in a matrix or having a mean particle size between 20 and 200 μm as recited in claim 1 or a mean particle size between 30 and 190 μm, or between 90 and 160 μm as recited in claims 4 and 5, respectively.

In order to overcome these deficiency in the teachings of WO 813, the Office Action alleges that '765 teaches a cosmetic transdermal patch for controlled delivery of water soluble and water insoluble active agents simultaneously where the water soluble drug particle range from 200 nm (0.2μm) to 500 μm.

According to the Office Action, it would have been obvious for one of skill in the art at the time of the instant invention to employ the water soluble ALA of WO 813 in the form of microparticles having a size range of anywhere between 200 nm to 500 μm in the polymer matrix taught by WO 813 because '765 allegedly suggests that a water soluble drug, which is otherwise stable in aqueous solution, may be added in the transdermal patch in a particulate form with a size of 200 nm to 500 μm. Applicants respectfully disagree.

A person of ordinary skill in the art would not combine WO 813 and '765 and arrive at claimed method

The goal in '765 was to combine water soluble and water insoluble drugs within the same transdermal patch. The solution provide by the patentees was to dissolve the water insoluble drug in oil and suspend the water soluble drugs as particles within the oil with a water absorbing agent. As such, the skilled artisan would only apply the teaching of '765 to ALA if they intended

to also add a water insoluble drug to the patch. Moreover, were they to make this combination, they would not omit the oil.

Applicants respectfully submit that either 1) the skilled artisan would have combined the cited references to arrive at a patch having ALA suspended in oil particles containing a water insoluble drug or 2) would not have combined the references at all.

In order to advance prosecution, Applicants have amended claim 1 to recite "A dermal application system, which is a self-adhesive matrix system, ***consisting of*** aminolaevulinic acid (ALA) derivative crystals suspended in a polymer matrix, wherein the polymer matrix ***consists of*** polymers from the group consisting of acrylates, silicon polymers, and polyisobutylene, ..." As amended, the claims no longer read on a polymer matrix containing oil, lipophilic drugs, or water-absorbing agents.

Based on the teachings of WO 813, the skilled artisan would have dissolved ALA in the polymers of a transdermal patch rather than suspending the ALA as crystals within the polymer matrix. Thus, the only reason the skilled artisan would have combined the teachings of WO 813 with '765 would be to combine ALA salt or ester with a drug that is insoluble in water (liposoluble) in the same transdermal patch. To do this, the skilled artisan would understand that the liposoluble drug would have to be dissolved in oil and the ALA salt or ester would have to be suspended as particles within that oil. In addition, particles of a water-absorbing agent, dispersed homogeneously in the polymer layer would need to be added to the polymer to provide water to the ALA salt or ester when the patch is added to the skin to dissolve the ALA salt or ester and make it bioavailable.

If, however, the skilled artisan did not intend to combine ALA salt or ester with a liposoluble drug, there would have been no motivation to combine WO 813 with '765.

Moreover, even if the skilled artisan found some motivation to combine these references without using a liposoluble drug, they certainly would not have omitted the oil and added ALA salt or ester to the polymer patch as a particle (crystal). Likewise, if the skilled artisan were motivated to add ALA salt or ester to a hydrophobic polymer, based the combination of the cited references they would not have omitted the oil or the water-absorbing agent.

Therefore, it would not have been obvious based on the combination of the cited references to produce a patch consisting of ALA salt or ester crystals suspended in a polymer matrix (i.e., not in aqueous solution) without the presence of at least oil. For at least this reason, Applicants respectfully request the withdrawal of this rejection.

The claimed dermal application system yields unexpected results

Moreover, Applicants have provided unexpected results that ALA releases from a transdermal patch at significantly higher rates when suspended as crystalline particles within the claimed size ranges as compared to ALA in solution.

Applicants submit with this response a Declaration under 37 C.F.R. § 1.132 by Mechtild Loebel affirming the statements made in the Declaration and Supplemental Declaration submitted to the United States Patent Office by Mechtild Loebel in U.S. Patent Application No. 10/332,547, filed September 30, 2003, which are referred to as "Loebel '547 Declaration" and "Loebel '547 Supplemental Declaration," respectively.

As was shown in Exhibit A of Loebel '547 Declaration and Exhibit B of Loebel '547 Supplemental Declaration, the rate of ALA crystal release is dramatically higher than what is observed in prior art dermal application systems using dissolved ALA.

About 9 $\mu g/cm^2$ ALA was released and had permeated through an artificial membrane (Loebel '547 Declaration). In contrast, about 515 $\mu g/cm^2$ ALA were released /permeated in the

first hour from a silicone patch containing suspended ALA crystals with a mean diameter of 90 to 160 μm (Loebel '547 Declaration). About 1,500 $\mu g/cm^2$ ALA were released in the first hour from a polyacrylate patch containing suspended ALA crystals with a mean diameter of 20 to 200 μm, with 72.5% of all ALA released in the first 30 minutes (Loebel '547 Declaration). Finally, about 1,000 $\mu g/cm^2$ (57 %) of ALA were released /permeated in the first hour from a polyisobutylen polymer patch containing suspended ALA crystals with a mean diameter of 90 to 160 (Loebel '547 Supplemental Declaration). Therefore, the rate of ALA release is dramatically higher when the ALA is suspended in the polymer patch as a crystal have with a mean diameter of 20 μm to 200 μm than when the polymer patch is prepared with dissolved ALA.

Applicants' evidence that crystalline ALA particles suspended in a polymer matrix (i.e., not in aqueous solution) have unexpectedly superior release rates over dissolved ALA is proper rebuttal evidence to demonstrate non-obviousness of the claimed composition. Applicants therefore respectfully request the withdrawal of this rejection.

Allowance of claims 1-2, 4-6, 9, 13 and 14, is respectfully solicited.

Transmitted herewith by Electronic Funds Transfer is $1,270.00, the fee for the Petition for a Three Month extension of time as a large entity. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-5226.

Respectfully submitted

McKEON MEUNIER CARLIN & CURFMAN, LLC

Date: June 13, 2012

/Brian Giles/

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Geoffrey Lee, et al.	Art Unit	: 1612
Serial No.	: 10/502,495	Examiner	: Maewall, Snigdha
Filed	: June 24, 2005	Conf. No.	: 5458
Title	: DERMAL APPLICATION SYSTEM FOR AMINOLEVULINIC ACID-DERIVATIVES		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, MECHTILD LOEBEL, hereby declare that:

1. I am an employee of photonamic GmbH & Co KG (further called "photonamic"), and hold a Ph.D. in Pharmacy from the University in Kiel, Germany. I have over 25 years of experience in the field of pharmaceutical development, with an emphasis on patch development in the last 9 years. At photonamic, I am responsible for all aspects of pharmaceutical development and report directly to the CEO.

2. Submitted with this Declaration are two Declarations submitted to the United States Patent Office by me in U.S. Patent Application No. 10/332,547, filed September 30, 2003. I hereby affirm all statements made in both of these Declarations.

3. The Declarations dated February 29, 2008, demonstrates that about 9 $\mu g/cm^2$ ALA was released and had permeated through an artificial membrane in the first hour from a silicone patch prepared with dissolved ALA. In contrast, about 515 $\mu g/cm^2$ ALA were released / permeated in the first hour from a silicone patch containing suspended ALA crystals with a mean diameter of 90 to 160 μm. About 1,500 $\mu g/cm^2$ ALA were released in the first hour from a polyacrylate patch

containing suspended ALA crystals with a mean diameter of 20 to 200 μm, with 72.5% of all ALA released in the first 30 minutes.

4. The Supplemental Declarations dated September 16, 2008, demonstrates that about 1,000 $\mu g/cm^2$ (57%) of ALA were released / permeated in the first hour from a polyisobutylen polymer patch containing suspended ALA crystals with a mean diameter of 90 to 160 μm.

5. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

06/13/2012
Date

M. Mechtild Loebel
MECHTILD LOEBEL

ATTORNEY DOCKET NO. 21127.0007U1
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Lee, et al.	)	Art Unit: 1615
	)	
Application No. 10/332,547	)	Examiner: Channavajjala, LS
	)	
Filing Date: September 30, 2003	)	Confirmation No. 5510
	)	
For: DERMAL APPLICATION SYSTEM FOR AMINOLEVULINIC ACID	)	

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEEDLE & ROSENBERG, P.C.
Customer Number 23859

Sir:

I, MECHTILD LOEBEL, hereby declare that:

1. I am an employee of photonamic GmbH & Co KG (further called "photonamic"), and hold a Ph.D. in Pharmacy from the University in Kiel, Germany. I have over 20 years experience in the field of pharmaceutical development, with an emphasis on patch development in the last 5 years. At photonamic, I am responsible for all aspects of pharmaceutical development and report directly to the CEO.

2. Photonamic is the assignee of the above-referenced application relating to dermal application system comprising crystalline aminolaevulinic acid (ALA). I coordinated the

experiments discussed herein, which were performed by one of the world's leading producer of dermal therapeutic systems on photonamic's behalf.

3. I have reviewed the Final Office Action mailed July 31, 2007 and the Advisory Action mailed December 21, 2007 in connection with the above-referenced application and the following references cited in that Office Action:

a) WO 95/05813 (WO), by Juan Mantelle and Allyn Golub, and

b) US 5,856,566 ('566), by Allyn Golub.

4. I understand that claims 1-6, 9 and 11-12 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over WO in view of '566. Specifically, I understand that the rejection is based in part on the contention that 1) WO teaches a pharmaceutical dermal application system comprising ALA and indicates a desire for the ALA preparation to be stable due to the normally rapid degradation of ALA, and 2) '566 suggests employing micronized crystals of ALA in order to overcome the degradation problem.

5. I present in this declaration evidence indicating that dermal application systems comprising ALA crystals in the size range of tens to hundreds of microns have a significantly and surprisingly higher rate of ALA release compared to a dermal application system with dissolved ALA, such as the system described in WO 95/05813 (WO). Figure 1 of **Exhibit A** (attached hereto) shows the release/ permeation profile of 5-ALA from a silicon polymer patch, wherein, in one case, a 5-ALA solution was incorporated, and in the other case, 5-ALA crystals with a size of 90-160 μm were suspended in the matrix. The determination of crystal size was carried out by sieving (see page 10, line 1 of the above-referenced application). The crystals

were ground and classified (see page 6, 3rd paragraph of Example 1), i.e., the size of crystals used was determined by sieving with a defined mesh size. Accordingly, particles sized 90-160 μm passed through a mesh size of 160 μm and did not pass through a mesh size of 90 μm. In this range, their distribution was approximately random.

As shown in Figure 1 of **Exhibit A**, a silicon polymer patch comprising ALA crystals in the size of 90-160 μm had a dramatically higher release rate compared to the dermal application system prepared with dissolved ALA ("dissolved ALA-patch"). After 1 hour, 9 $\mu g/cm^2$ was released and had permeated through an artificial membrane when the dissolved ALA-patch was used, while 515 $\mu g/cm^2$ was released/ permeated from the patch comprising ALA crystals. Of note, the release/ permeation rate measured for the dissolved ALA-patch (9 $\mu g/cm^2$) was even higher than that disclosed by the WO reference, which states that the release rate should be at least 0.1 $\mu g/cm^2$ per hour.

As can be seen from Figure 2B of **Exhibit A**, ALA crystals from approximately 20 to 200 μm in size were used for preparation of a polyacrylate patch. As shown in Figure 2A of **Exhibit A**, the release rate was about 1500 $\mu g/cm^2$ of ALA in the first hour, with 72.5 % of all ALA released in the first 30 min.

6. I further declare that the demonstrated effect of significantly increasing the release rate by dispersing ALA crystals of a size of 30-200 μm in a dermal application system was not foreseeable on the basis of WO and '566.

7. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the

statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 29.02.2008

M. Loebel

MECHTILD LOEBEL

EXHIBIT A

Figure 1:

Release / permeation profile of ALA from a silicon polymer patch (BioPSA®) through an artificial membrane. The patches were manufactured by two different methods: for the first method ("dissolved", containing 15% ALA) an ALA-solution was incorporated in the matrix and then the patches were prepared. For the second method ("suspended", containing 20% ALA) a matrix with suspended ALA particles sized 90-160 µm was used.

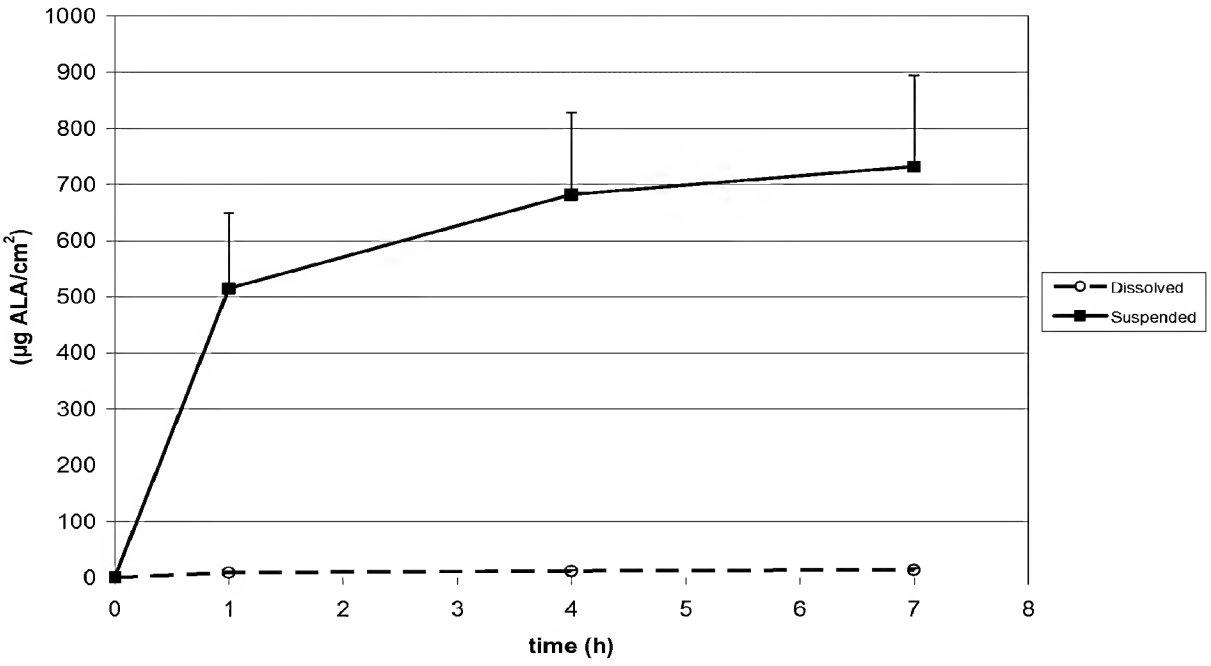


Figure 2A shows release profile of ALA from a polyacrylate patch (DuroTak®). Patches were prepared using ALA particles, passed through a 200 μm sieve, suspended in the matrix. Within 30 minutes 72,5 % of all ALA was released.

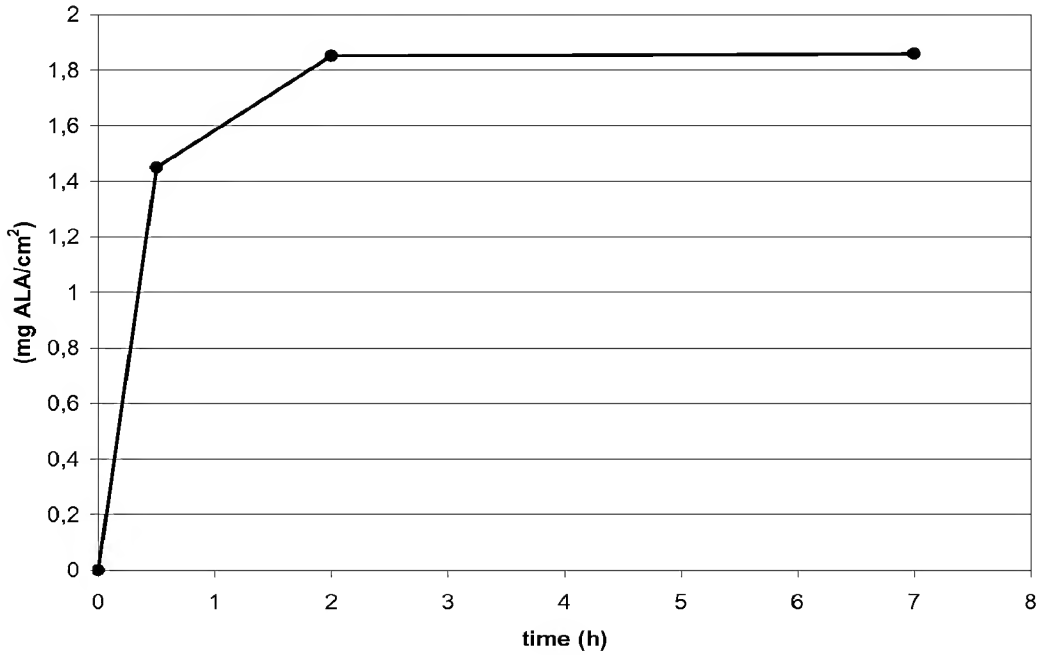
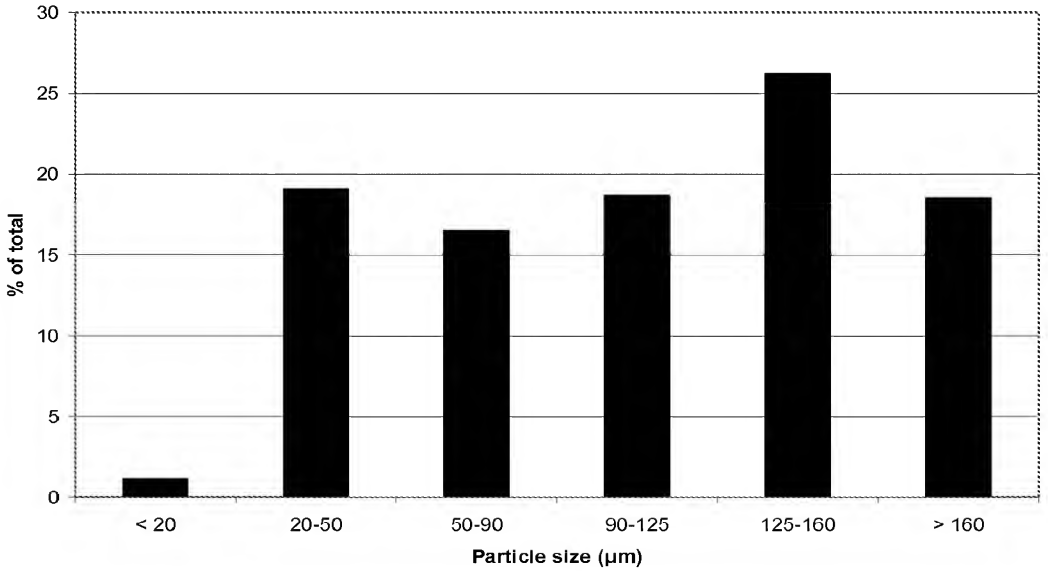


Figure 2B shows particle size distribution of the batch of ALA used for patches of Figure 2A.



ATTORNEY DOCKET NO. 21127.0007U1
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Lee, et al.	)	Art Unit: 1615
	)	
Application No. 10/332,547	)	Examiner: Channavajjala, LS
	)	
Filing Date: September 30, 2003	)	Confirmation No. 5510
	)	
For: DERMAL APPLICATION SYSTEM FOR AMINOLEVULINIC ACID	)	

SUPPLEMENTAL DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEEDLE & ROSENBERG, P.C.
Customer Number 23859

Sir:

I, MECHTILD LOEBEL, hereby declare that:

1. I am an employee of photonamic GmbH & Co KG (further called "photonamic"), and hold a Ph.D. in Pharmacy from the University in Kiel, Germany. I have over 20 years experience in the field of pharmaceutical development, with an emphasis on patch development in the last 5 years. At photonamic, I am responsible for all aspects of pharmaceutical development and report directly to the CEO.

2. Photonamic is the assignee of the above-referenced application relating to dermal application system comprising crystalline aminolaevulinic acid (ALA). I coordinated the experiments discussed herein, which were performed by one of the world's leading producer of dermal therapeutic systems on photonamic's behalf.

3. I present in this declaration evidence indicating that dermal application systems comprising ALA crystals in the size range of tens to hundreds of microns have a significantly and surprisingly higher rate of ALA release compared to a dermal application system with dissolved ALA, such as the system described in WO 95/05813.

As shown in Exhibit A submitted with the prior Declaration, 515 $\mu g/cm^2$ ALA were released/ permeated from a silicon polymer patch comprising ALA crystals (90-160 μm) in the first hour, whereas only 9 $\mu g/cm^2$ ALA was released and had permeated through an artificial membrane when the dissolved ALA was used (see Figure 1 of Exhibit A). Likewise, about 1500 $\mu g/cm^2$ of ALA were released/ permeated from a polyacrylate patch comprising ALA crystals (20 to 200 μm in size) in the first hour, with 72.5 % of all ALA released in the first 30 min (see Figure 2A of Exhibit A). Moreover, as shown in Figure 1 of **Exhibit B** (attached hereto), about 1000 $\mu g/cm^2$ (57%) of ALA were released/ permeated from a polyisobutylen polymer patch comprising ALA crystals (90-160 μm) in the first hour. Therefore, the rate of ALA crystal release is dramatically higher than what is observed in prior art dermal application systems using dissolved ALA. Moreover, these results indicate that the unexpectedly higher ALA release rates are independent of the polymer matrix used.

4. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such

willful false statements may jeopardize the validity of the application or any patent issuing thereon.

5. I further declare that the demonstrated effect of significantly increasing the release rate by dispersing ALA crystals of the defined size in a dermal application systems such as a polyisobutylen patch, was not foreseeable on the basis of WO 95/05813 and/or US 5,856,566 .

Date: 16.09.2008

M. Loebel

MECHTILD LOEBEL

EXHIBIT B

Figure 1:

Release / permeation profile of ALA from a polyisobutylen polymer patch (Oppanol®) through an artificial membrane. Patches were prepared using ALA particles sized 90-160 µm suspended in the matrix. Within one hour 57 % of all ALA was released.